REMARKS

Entry of the preceding amendments and consideration of the comments which follow are respectfully requested by Applicants.

Amendments to claims

Claims 4-11 and 23-26 have been canceled as withdrawn. Claim 1 is amended to clarify that all steps must be performed on the array in accordance with the present invention and to clarify that "couple" within the meaning of the present claim means to directly couple. That is, indirect linkages are not within the scope of the instant coupling language. Support for this amendment is found throughout the specification, e.g., paragraphs [0018], [0019], and [0004] and as disclosed in all exemplary embodiments whereby direct coupling of the protecting group and nucleobase is illustrated. Claim 22 is amended to clarify the relationship between each recitation of "analog" and the compound to which it is related in accordance with teachings found at paragraph [0030] of the instant specification. No new matter has been added.

Claims 1-3, 12, 13, and 15-22 remain pending and subject to examination.

Rejection under 35 USC §112, first paragraph

Claim 22 is rejected as failing to comply with the written description requirement and, more particularly, for an alleged recitation of new matter not supported by the original disclosure. Specifically, the Examiner notes the amendment to claim 22 and objects that the recitation may be reasonably interpreted to mean analogs of "aza analogs" and "diaza analogs" and that such "analogs of analogs" do not appear to have support in the specification. This rejection is traversed, and reconsideration is respectfully requested.

Instant claim 22, as amended, recites the method of claim 15 wherein B is selected from the group consisting of adenine (A), guanine (G), cytosine (C), aza analogs of A, G and C, deaza analogs of A, G and C, combination aza and deaza analogs of A, G, and C, and analogs thereof containing additional amino groups.

Support for this amended claim may be found in the specification at paragraph [0030]. In accordance with this disclosure, B may be one of the three nucleobases, aza analogs of any of those bases, diaza analogs of any one of those bases, or combination aza and diaza analogs of any one of those bases (see

paragraph [0030], page 9, line 3 for disclosure of this specific embodiment). Further, in accordance with paragraph [0030], lines 6-9, any of the nucleobases or analogs discussed in the preceding portion of the paragraph are included within the subsequent recital of "Further, suitable nucleobase analogs may carry additional amino groups." Applicants submit that this language reasonably intends to include any of the nucleobases or aza and diaza nucleobases with additional amino groups, as interpreted by the Examiner with respect to the claim language itself. Hence, Applicants submit that the claim, as amended, has one reasonable interpretation in light of the specification and that written support exists for this interpretation. Reconsideration is therefore respectfully requested.

Rejection under 35 USC §102

Claims 1-3, 12, 13, and 15-22 are rejected under 35 USC §102(b) as being anticipated by Wagner et al., *Helv. Chim. Acta. 80*:200-212, 1997 ("Wagner"). Specifically, the Examiner re-asserts reasons of record including arguments that Wagner discloses methods of nucleic acid synthesis using protected nucleotides and teaches synthesis of various oligonucleotides using protected nucleotides, deprotection of the nucleotides through removal of the protecting groups, and kinetic studies of the deprotection process, as well as use of a fluorescent label as a detectable label that may be linked directly to the nucleobase through the amino group. In response to Applicants' prior traversals, the Examiner further asserts that "the instant claims do not specifically recite a method of fluorescent detection," and that the features upon which Applicants rely to distinguish their invention are not recited in the rejected claims. In particular, the Examiner asserts that the language of instant claim 1 "does not necessarily dictate that the signal detection step is carried out 'on the array.'"

Instant claim 1 is directed to a quality control method for manufacturing a biopolymer array. The method comprises (a) synthesizing a plurality of different biopolymer species on an array from monomeric or oligomeric building blocks comprising detectable protecting groups, (b) cleaving off the detectable protecting groups, and (c) carrying out a determination of the degree of deprotection by detecting detectable protecting groups remaining on the array after cleavage, wherein steps (a), (b), and (c) are performed on the array and wherein at least some of the detectable protecting groups directly couple to and protect nucleobase amino groups.

Once again, Applicants acknowledge that Wagner discloses a nucleobase amino protecting group but reiterate that the protecting group may or may not exhibit detectable fluorescence. Whether or not the chlorinated dansyl of Wagner exhibits detectable fluorescence as required by the instant claims is a question apart from whether it fluoresces to any degree or under particular circumstances/conditions.

Wagner fails to teach potential fluorescent properties or provide a motivation for detectable fluorescence of this compound and does not indicate that the protecting group is detectable via any quantity of fluorescence that may be characteristic of this group. Applicants submit that the Examiner offers no support for the contention that dnseoc either fluoresces or fluoresces to any extent detectable for purposes of the present methods.

Further, as noted previously, the kinetic studies of Wagner, cited by the Examiner as equivalent to step (c) of instant claim 1, rely on typical HPLC technology, which is not suitable for the on-chip or "on the array" analysis required by instant claim 1. Applicants submit that instant claim 1, as amended, makes it clear that this step must occur on the array, or chip, in accordance with the present invention. Applicants submit that the amendment overcomes the alleged uncertainty as to whether this step must be performed on the chip. Applicants expressly distinguish the present invention over the teachings of Wagner, noting that the present invention provides the capability of quality control with respect to completeness of deprotection of the biopolymer active sites on the chip without destruction of any biopolymer and without the need for further steps once the final deprotection or detection has been carried out (see, e.g., paragraphs [0005] and [0007]).

Wagner discloses base amino protection for the purpose of accelerating the cleavage process and increasing the *rate* of deprotection. Wagner measures the efficacy of the protecting groups in achieving this goal by performing HPLC of the crude oligonucleotide. The detection step of Wagner, therefore, occurs off the array and involves consumption of the biopolymer in direct contravention to the goals of the present invention. Further, the methods of Wagner merely yield a cleavage (deprotection) reaction half-life and are not concerned with determining the completeness of the deprotection method. A reaction half-life as a parameter fails to provide any information on either the rate of deprotection *at the end of the synthesis* or the completeness of the deprotection overall. A person of ordinary skill in the art would understand that in the absence of characterization of the rate mechanics of the reaction as deprotection proceeds toward greater accumulation of the deprotection products, there is no way to extrapolate from a known half-life any information regarding completeness of the deprotection at the end of the synthesis.

Wagner merely teaches a method for deprotecting that enables use of a B-elimination reaction as the deprotecting mechanism and thereby assertedly achieves more rapid deprotection. Quality control of ***on-array*** or ***on-chip*** synthesis with respect to achieving deprotection is not disclosed, addressed, or suggested.

Anticipation under 35 USC §102(b) requires the disclosure in a single prior art reference of each element of the claims under consideration, *Alco Standard Corp. v. TVA*, 1 USP.Q.2d 1337, 1341 (Fed. Cir. 1986). Wagner fails to disclose quality control methods comprising, inter alia, carrying out a determination of a detectable protecting group ***on the array*** after cleavage. The methods of Wagner rely on off-chip technologies for analysis of the oligonucleotide product to determine a rate of deprotection, resulting in the undesirable consumption of the product sought to be avoided by the present invention. Since Wagner fails to disclose all the limitations of claim 1 and fails to disclose methods which could effectuate the purpose of the present invention as defined by claim 1, Wagner does not anticipate instant claim 1 nor any claims dependent therefrom. The rejection of claims 1-3, 12, 13, and 15-22 under 35 USC §102(b) under Wagner is therefore overcome. Reconsideration is respectfully requested.

Rejection under 35 USC §103

The rejection of **claims 1-3, 12, 13, and 15-22** under 35 USC §103(a) as being unpatentable over Wagner in view of Hobbs et al., US 5,151,507 ("Hobbs") and, if necessary, further in view of Chen et al., *Journal of Organic Chemistry 66*:1725-1732, 2001 ("Chen") is maintained for reasons of record. The Examiner applies Wagner for the disclosure set forth above but notes that Wagner fails to teach "stilbene" as the fluorescent group as recited in claim 3. The Examiner asserts that Hobbs teaches the use of various fluorescent molecules "to label or protect" nucleotides and specifically teaches that stilbene can be used to attach to nucleobases through linkers comprising carbonyl groups, assertedly in accordance with instant claim 21, and generally teaches various fluorescent dyes which can be used depending on intended application. The secondary reference, Chen, is applied for the teaching that stilbene has a "bright fluorescence of very high quantum yield." The Examiner combines these references to conclude that it would have been *prima facie* obvious for one of ordinary skill in the art to attach a fluorescent group such as stilbene to a monomeric building block such as a nucleoside to form the detectable protecting group of the present invention with a reasonable expectation of success for achieving the attachment since the references teach successful attachment of various fluorescent groups, including stilbene, to nucleosides through known reaction mechanisms.

In response to Applicants' previous traversal, the Examiner once again argues that the instant detection step of claim 1(c) is not necessarily carried out on the array and that claim 1 may be reasonably interpreted to mean detecting the detectable protecting groups that were cleaved off in step (b). This rejection is traversed, and reconsideration is respectfully requested.

The recitation of independent claim 1, directed to quality control methods for manufacturing a biopolymer on an array, is set forth in detail above. In pertinent part, the method comprises (c) carrying out a determination of the degree of deprotection by detecting detectable protecting groups remaining on the array after cleavage wherein steps (a), (b), and (c) are performed on the array.

Applicants submit that, as amended, instant claim 1 makes it clear that the determination of the degree of deprotection is achieved on the array. As noted in paragraphs [0018] and [0019], the detectable protecting groups remain on the biopolymer until synthesis is terminated. A "first determination" is made prior to cleavage, cleavage is instigated, and additional determinations are made to detect the degree of deprotection (see, e.g., paragraph [0020]).

Wagner, on the other hand, discloses methods for determining an initial rate of deprotection but fails to teach or suggest methods for determining rates or quantifying deprotection products that permit such determinations **on the array** as required by instant claim 1. The present invention provides superior quality control methods because it enables determination on the chip without interfering with synthesis of the biopolymer, without consuming the biopolymer product, and without requiring any additional post-determination steps. The methods of Wagner require removal of biopolymer and/or other reagents from the array and analysis by HPLC, which consumes some of the product. Wagner determines the rates of deprotection by halting the synthesis at various points and quantifying reagents across synthesis, which may be plotted to yield a curve from which a reaction half-life is obtained. The methods of Wagner reflect the inferior methods sought to be improved upon by the present methods, which enable on-chip analysis and which do not interfere with synthesis on the chip.

The secondary references do not overcome the deficiencies of Wagner. Hobbs is directed to certain labeled nucleotides useful as chain-terminating substrates for DNA sequencing and discloses the use of stilbene as one label. Hobbs fails to teach or suggest quality control methods applicable to biopolymer array synthesis and fails to disclose any methods comprising determination of detectable protecting groups on an array in order to determine efficacy of deprotection. Assuming there is any motivation to import the fluorescing stilbene label of Hobbs into the methods of Wagner, the result is merely a different protecting group subject to the same off-chip HPLC analysis of Wagner, and the combination fails to achieve the present inventive methods which are concerned with, inter alia, the degree of deprotection achieved at the end of synthesis. The secondary reference, Chen, directed to the properties of stilbene as a fluorescent label, is completely inapposite to overcoming the deficiencies of Wagner.

To establish prima facie obviousness of the claimed invention, all the claim limitations must be taught or suggested by the prior art, *In re Royka*, 490 F.2d 981, 180 USP.Q. 580 (CCPA 1974). In order to render a claimed invention obvious, the prior art must enable one skilled in the art to make and use the claimed invention, *Motorola, Inc. v. Interdigital Tech. Corp.*, 43 USP.Q.2d 1481, 1489 (Fed. Cir. 1997). The combination of Wagner, Hobbs, and Chen fails to teach or suggest quality control methods for manufacturing a biopolymer on an array capable of being performed ***on the array*** without interfering with the synthesis of the biopolymer species and without additional steps required after carrying out the quality control step of determining efficacy of deprotection. The methods of Wagner, taken with the teachings of Hobbs and Chen regarding labels, do not enable the present inventive methods, as Wagner subjects the oligonucleotides and deprotection products to analysis via HPLC and never suggests analytical technology that enables determination on the array. The present inventive method, as opposed to the method resulting from the combination of references as asserted by the Examiner, assesses quality of the array at the end of synthesis, does not interfere with synthesis, and does not require any further processing of the array before it may be used in subsequent applications.

Hence, the rejection of claim 1 and claims 2, 3, 12, 13, and 15-22 dependent therefrom as being unpatentable under 35 USC §103 over Wagner in view of Hobbs and Chen is overcome. Reconsideration is respectfully requested.

Claims 1-3, 12, 13, and 15-22 are rejected under 35 USC §103(a) as being unpatentable over US Patent No. 6,238,862 to McGall ("McGall") and Wagner in view of Hobbs and, if necessary, Chen. Specifically, the Examiner asserts that McGall teaches synthesizing nucleic acids using protected monomers, removal of the protecting groups, and determining the amount of unprotected active sites by detecting the amount of cleaved detectable label. The Examiner further asserts that McGall teaches that a protecting label is a fluorescent label such as rhodamine and that the label is linked to the nucleoside. The Examiner contends that the instant recitation of "coupled" may be broadly interpreted to include coupling through any type of linkage including both direct and indirect linkages so that linkage via the sugar group, as disclosed in McGall is within the scope of "coupling" to the nucleobase of the nucleotide. The Examiner notes, however, that McGall fails to expressly teach coupling of the protection groups to protect the nucleobase amino groups. The Examiner asserts Wagner for disclosure of a fluorescent label linked directly to the nucleobase through amino groups in oligonucleotide synthesis. The Examiner concludes that a person of ordinary skill in the art would be motivated to couple the protection groups to the amino groups of the nucleobase because the nucleobase protection offers the advantages of providing more efficient and fast-working synthesis, as taught by Wagner. The other references are applied for

asserted disclosure of various dependently recited elements. This rejection is traversed, and reconsideration is respectfully requested.

The recitation of claim 1 is set forth in detail above. In pertinent part, claim 1 requires that at least some of the detectable protecting groups directly couple to and protect nucleobase amino groups. The protecting groups of the present inventive methods, therefore, directly couple to the nucleobase and do not interfere with synthesis. The protecting groups are not cleaved until after synthesis of the plurality of oligonucleotides forming the array. Degree of deprotection is therefore not ascertained until synthesis of the array is complete.

McGall, on the other hand, only teaches linkage of protecting groups via the 5-hydroxyl active site of the sugar terminus. The terminus is required for the next step in the synthesis such that cleavage of the protecting group must occur at each step of the synthesis, that is, at the addition of each nucleobase to the oligonucleotide. According to the present methods, the protecting groups couple directly to the nucleobase and do not need to be removed until complete synthesis of the oligonucleotide is achieved. This reduces steps, increases automative capacity, and reduces error. This difference is not trivial under several considerations. For example, since the protecting groups of the present invention are directly coupled to each nucleobase at an active site not implicated in oligonucleotide synthesis, fluorescence from the oligonucleotide increases proportionally with the addition of each nucleobase, thus providing potential for feedback as to completion of synthesis of the desired oligonucleotide array. However, since McGall removes the labeled protecting steps at each nucleobase addition, McGall fails to provide such feedback potential. In addition, in accordance with the present methods, overall fluorescence is measured at the completion of synthesis, whereafter cleavage is instigated and fluorescence is re-measured, providing a degree of deprotection with respect to the overall synthesis. According to McGall, however, deprotection is measured merely by absence of fluorescence and must be measured at every step.

As noted above, the secondary reference Wagner is inapposite to the comparison of quality control methods restricted to on-array or on-chip analysis. Wagner fails to teach any on-array determination of degree of deprotection and fails to overcome the deficiencies of the primary reference with respect to direct coupling of the protecting group and nucleobase and with respect to cleavage of the protecting group upon completion of the array synthesis. The other secondary references, applied for various disclosures of dependent elements, fail to address or overcome this deficiency as well.

Hence, claims 1-3, 12, 13, and 15-22 are nonobvious and patentable over the combination of McGall, Wagner, Hobbs, and Chen, and the rejection under 35 USC §103 over these references is overcome. Reconsideration is respectfully requested.

Conclusion

Applicants submit that their application is now in condition for allowance, and favorable reconsideration of their application in light of the above amendments and remarks is respectfully requested. Allowance of claims 1-3, 12, 13, and 15-22 at an early date is earnestly solicited.

* * * * * *

The Commissioner is hereby authorized to charge any fees associated with this Amendment to Deposit Account No. 02-2958.

Respectfully submitted,

Marilyn L. Amick
Reg. No. 30,444

Customer No.: 23690
Phone: 317-521-7561
Fax: 317-521-2883